APPLICANTS: Comb *et al.*
U.S.S.N.: 09/535,364

REMARKS

This Amendment and Response is filed following receipt of the first Office Action on the merits in the present case, which Office Action included a final restriction requirement after Applicants' previous provisional election with traverse. Applicants acknowledge that claims 19, 21, 22, and 34-38 have been withdrawn from consideration. Following a telephone conversation with the present Examiner and SPE Andrew Wang regarding the final restriction requirement made by the previous Examiner, claim 27 has been voluntarily canceled in favor of pursuing certain preferred subject matter of independent genus claim 28 (and claims dependent thereon) in the present application. The present Examiner indicated in that conference call that genus claim 28 would not require further restriction. New independent claim 39, also discussed in conversation with the Examiner and SPE Wang, has been added. A typographic error has been corrected in claim 32. No other claim amendments have been made. Upon entry of the present amendments, claims 28-33 and 39 are pending.

Applicants submit that all of the concerns and rejections raised by the previous Examiner have presently been overcome (as set forth in detail below), and respectfully request that the claims be promptly advanced to allowance.

Applicants have amended the "Abstract" of the specification, on pages 59-60, to conform to the size requirements of 37 C.F.R. §1.72(b). Line 25, second paragraph of page 34 of the specification has also been amended to correct a typographical error ("-1" should read "+1"), as suggested by the previous Examiner. Support for this amendment is found throughout the specification as originally filed, *e.g.* in Figure 1D at the thirteenth row. Applicants have voluntarily cancelled claim 27, as noted above, to pursue and expedite prosecution of the preferred subject matter of independent genus claim 28 in the present application. In accordance with the previous Examiner's suggestion, claim 32 has been amended to correct a minor typographic error in the last line ("with" should read "within"). Lastly, new claim 39 has been added, as discussed with the present Examiner, and is drawn to a preferred species (a phospho-threonine specific antibody) of the disclosed class of motif-specific, context-independent antibodies. Support for this amendment is found throughout the specification, as originally filed, *e.g.* at p. 27, lines 10-18, including the claims as originally filed. These amendments do not introduce new matter.

Applicants acknowledge that the previous Examiner has considered the references cited and disclosed in the previously filed Information Disclosure Statement.

RESTRICTION REQUIREMENT

The previous Examiner has made final the restriction requirement pertaining to the elected claims of Group V (claims 27-29 (in part), 30, 31, 32 (in part) and 33) and Groups VI-VIII, alleging that – despite having the same class and subclass – the subject matter of these groups would require different searches requiring combinations of sub-terms and would thus be unduly burdensome. Applicants have previously traversed and requested reconsideration on the ground that the subject matter of the claims of Group VI (insofar as relating to phosphorylated kinase consensus substrate motifs) and VII (insofar as relating to phosphorylated protein-protein binding motifs) is not independent and distinct, but rather shares a common function, feature and effect. *See* MPEP §806.04(e).

Applicants have presently voluntarily canceled independent claim 27 (drawn to antibodies binding a modified signaling motif containing at least one phosphorylated, acetylated, or methylated residue) in order to focus on, and expedite prosecution of, the preferred subject matter of genus claim 28 (drawn to antibodies binding a kinase consensus substrate motif, or protein-protein binding motif, containing at least one phosphorylated amino acid). The provisional election of the species Akt consensus substrate motifs within the genus defined by claim 28 is acknowledged.

In a tele-conference with SPE Andrew Wang and the present Examiner, Applicants' attorney reiterated that phosphorylated kinase consensus substrate motifs and phosphorylated protein-protein binding motifs relevant to signal transduction are structurally similar and share common characteristics: both contain one or more fixed (*i.e.* required) residues, including one or more phosphorylated (or phosphorylatable) residues, and often one or more variable (*i.e.* degenerate) residue positions together comprising a short (typically two to eight amino acids) motif; both occur in multiple proteins within a genome that are involved in signal transduction cascades (*e.g.* many different substrate proteins containing the same consensus motif may be enzymatically modified by a single kinase). Accordingly, motif-specific, context-independent antibodies of the invention that bind these respective motifs share a common essential feature,

function, and effect. Applicants' attorney emphasized that the subject matter of genus claim 28 is in one class and one subclass, are in the same field, and would not require separate searches. MPEP §808.02. Accordingly, the subject matter of claim 28 is a genus not requiring further restriction, and the subject matter of dependent claim 29 recites certain preferred species within the genus.

The present Examiner has indicated, in the tele-conference, that further restriction of genus claim 28 is not required, and that prosecution on the merits of this genus claim can advance. 37 C.F.R. §1.141(a). Accordingly, withdrawal of the restriction requirement pertaining to pending claims 28-33 is respectfully requested.

The Examiner has also indicated that Applicants' may add new claim 39 (drawn to a preferred and particular species of disclosed context-independent antibody; namely, one that binds a single phospho-threonine residue), since this subject matter is in the same class/subclass and field as the subject matter of claim 28, would not require separate search, and is not independent and distinct from the claimed subject matter.

OBJECTIONS TO SPECIFICATION & CLAIMS

The previous Examiner has objected to claim 32 for containing a typographic error, and has required that "with" in the last line of the claim be changed to "within." Accordingly, Applicants have made this correction to claim 32. This minor typographic correction does not introduce new matter.

The previous Examiner has also objected to the length and content of the Abstract. Accordingly, Applicants have amended the Abstract of the specification, on pages 59-60, to conform to the size and brevity requirements of 37 C.F.R. §1.72(b). Support for this amendment is found in the original Abstract and throughout the specification as originally filed, and the amendment does not introduce new matter.

Lastly, the previous Examiner has noted that on page 34 of the specification, last paragraph, it appears that "in –1 position by proline" should be "in +1 position by proline." The Examiner has correctly noted this typographic error. Accordingly, line 25, second paragraph of page 34 of the specification has been amended to correct this minor error ("-1" now reads "+1"),

as suggested by the previous Examiner. Support for this amendment is found throughout the specification as originally filed, *e.g.* in Figure 1D at the thirteenth row. This amendment does not introduce new matter.

Brief Overview of Motif-Specific, Context-Independent Antibodies.

In order to assist the present Examiner in better understanding the claimed subject matter, the following brief overview of the antibodies of the invention (as described in detail in the Specification) is provided to aid the Examiner in her consideration of Applicants' responses to the outstanding claim rejections.

Applicants' invention provides, in part, a novel class of antibodies that are *both* motif-specific and context-independent (*see, e.g.*, specification at p. 13, lines 21-26; p. 8, lines 5-14). The antibodies of the invention are designed to, and are capable of, recognizing short modified signal transduction motifs -- *e.g.* kinase consensus substrate motifs, protein-protein binding motifs, single phospho-residues, etc. -- that occur in multiple different peptides or proteins within a genome. These powerful and novel reagents provide, for the first time, the ability to simultaneously examine the modification statuses of multiple signaling proteins (containing a conserved motif) expressed within the genome of an organism using a single antibody (*see, e.g.*, specification at p. 21, lines 5-10), and thus solve the limitations of prior antibodies, including typical peptide- or site-specific antibodies, described in the Background of the Invention at p. 2-6. This powerful class of antibodies are proving to be extremely useful in, *inter alia*, profiling the signal transduction events driving human disease, and in identifying new targets for a new generation of targeted therapies to treat diseases like cancer.

§112, 1ST PARAGRAPH, WRITTEN DESCRIPTION REJECTIONS

The previous Examiner has rejected claims 27-33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not adequately described in the specification. The previous Examiner asserts that the specification does not indicate that Applicants were in possession of the claimed invention because the scope of the claims allegedly includes "thousands of motifs" from "thousands of different species," that the "predictability that antibodies can be raised" is low, and that the working examples provided in the specification are

not "representative of the antibodies encompassed by the present claims." (See Feb. 25th Office Action at p. 4-5). Applicants disagree, and respectfully submit that the previous Examiner has failed to meet his burden of establishing a *prima facie* case (supported with evidence) of inadequate written description. In stark contrast, the extensive description provided in the specification readily shows that Applicants were in possession of the claimed subject matter.

It is black letter law that "possession" of a claimed invention for purposes of satisfying the written description requirement of 35 U.S.C. 112, 1st paragraph, is shown by describing, in the specification, the claimed invention with all of its limitations. *See* MPEP §2163(I), *citing Lockwood v. American Airlines* (Fed. Cir. 1997). Among other ways, possession may be shown by actual reduction to practice, or by describing the distinguishing characteristics of the claimed invention. *See Id., citing Pfaff v. Wells Elecs.* (Sup. Ct. 1998). The description of distinguishing characteristics must indicate to a person skilled in the art (not to the Examiner) that the inventor possessed the claimed subject matter. *See* MPEP §2163(3)[a], *citing Purdue Pharma L.P. v. Faulding* (Fed. Cir. 2000); *see also* MPEP §2163.02.

With respect to a genus claim, no magic number of species need be described to satisfy the written description requirement. Rather, the assessment of whether a "representative number" of species having the distinguishing characteristics and common elements of the claimed genus has been described in the specification remains in the eyes of – and from the standpoint of -- the skilled artisan. What constitutes a "representative number" of species is an inverse function of the skill and knowledge in the art; in well developed areas of technology (like antibody production) where the level of skill is high, the technique well established and predictable, only a few exemplary species need be described to show possession of a genus. *See* MPEP §2163(3)[a](ii), citing *Regents of U. of Cal. v. Eli Lilly* (Fed. Cir. 1997), and MPEP §2163(II)[A](ii), *citing Hybritech v. Monoclonal Antibodies* (Fed. Cir. 1986); *see also Utter v. Hiraga*, 845 F.2d 993 (Fed. Cir. 1988) (a specification may contain sufficient written description of a broadly claimed invention without describing all species the claim encompasses).

There is *a strong presumption* that an adequate written description of the claimed invention is present when the application is filed. *See* MPEP§2163(A), *citing In re Wertheim* (CCPA 1976). *The initial burden is on the Examiner* to present evidence or reasons why a person skilled in the art would not recognize that an applicant is in possession of the claimed

invention. *See* MPEP §2163(II)[A]; MPEP §2163.04. An Examiner must carry this burden by a preponderance of the evidence, and must set forth express findings of fact to support an allegation of inadequate written description. *See Id.* A general allegation of "unpredictability in the art" is not a sufficient reason to make or support a written description rejection. *See Id.*

Here, the previous Examiner has made just such a general and unsupported allegation. The previous Examiner has failed to provide *any* evidence or facts (much less a preponderance) supporting why one of ordinary skill in the well-developed and predictable art of making anti-peptide antibodies would not recognize in Applicant's disclosure a description of the claimed invention. No express findings of *fact* have been presented. Indeed, in making this cursory rejection, the previous Examiner appears to have failed to even consider the USPTO's own Revised Interim Written Description Guidelines (http://www.uspto.gov/web/patents/guides.htm), which, in discussing antibody claims and technology (at p. 52, Example 16), clearly states that antibody structure and function is well characterized and that antibody production is a mature technology where the level of skill is high and advanced. Accordingly, the previous Examiner has failed to establish a *prima facie* case of inadequate written description. The rejections are improper, and should therefore be withdrawn.

Moreover, a thorough review of the disclosure and recognition of the high level of skill and predictability in the art of antibody production readily indicates that Applicants have satisfied the written description requirement of 35 U.S.C. §112, 1st paragraph. The presently claimed invention, in its broadest sense (*see* claim 28, as amended), is a genus of antibodies having the following defining features: their binding affinity is "motif-specific" but also "context-independent," they bind either a "kinase consensus substrate motif" or a "protein-protein binding motif," the bound motif comprises "at least one phosphorylated amino acid", and they bind (*i.e.* recognize) a "plurality of peptides or proteins within a genome that contain [the] motif."

Each of these defining elements or characteristics of the claimed invention is thoroughly described in the specification. The production of this class of antibodies is described in detail, step-by-step (including testing for desired specificity and context-independence), for both poly- and monoclonal antibodies, at p. 14-19. The types of motifs against which antibodies of the invention may be raised are described throughout the specification, for example at p. 7, line 16 to

p. 8, line 14; p. 19, line 21 to p. 20, line 26; p. 1, line 15, to p. 2, line 18, and Examples I-VIII. The context-independence of this class of antibodies (*i.e.* their ability to recognize many different peptides or proteins containing a short conserved target motif) is well described throughout the specification, for example at p. 13, lines 4-26; p. 16, line 24 to p. 18, line 19; p. 24, line 16 to p. 26, line 24, and the Examples. The structure of typical kinase consensus substrate motifs and protein-protein binding motifs bound by the claimed antibodies are well described in Examples II-IV and VI-VIII, as well as, for example, at p. 7, line 25 to p. 8, line 14, and p. 2, lines 6-18. Exemplary phospho-amino acids that may be part of the motif for which the claimed antibodies are specific are described throughout the specification, including at p.7, lines 16-24. Lastly, the functional ability of the claimed antibodies to bind a plurality of targets within a genome containing the desired motif is extensively described throughout the specification, for example, at p. 8, lines 16-22; p. 19, line 21 to p. 26, line 24 generally; p. 6, line 5 to p.7, line 12; and the Examples. Applicants have thus described the essential features and distinguishing characteristics of the claimed invention in sufficient detail to show possession of the claimed subject matter to one of skill in the art of anti-peptide antibody production. *See* MPEP §2163(3)[a]; §2163(3)[a](ii), and cases cited above.

Further, the specification provides no less than eight working examples of the claimed class of antibodies, which Examples include both polyclonal and monoclonal antibodies. Examples II-IV and VI-VIII exemplify species of motif-specific, context-independent antibodies that bind phosphorylated kinase consensus substrate motifs or protein-protein binding motifs. These exemplary signal transduction motifs range from 2 to 6 amino acids long, include different types of phosphorylated amino acids, and describe the structure of typical amino acid motifs (including degenerate motifs) bound by the claimed genus of antibodies. Examples I and V exemplify species of motif-specific, context-independent antibodies that bind single modified residues (phospho-residues and acetylated-residues, respectively). The context-independent antibody of Example I (which binds a single phosphothreonine residue) is the subject of independent claim 39.

Applicants have provided these eight detailed working examples of a representative number of antibodies further describing the common elements and features of the claimed class of antibodies, despite the fact that the production, characterization, structure, and functions of

antibodies, including anti-peptide antibodies, are extensively developed and well known in the art (*see, e.g.*, Czernik (1991) and Czernik (1995), cited in Background of Invention on p. 5, line 21; ANTIBODIES: A LABORATORY MANUAL, Chapter 5, p. 75-76, Harlow & Lane Eds., Cold Spring Harbor Laboratory (1988); Kohler and Milstein, *Eur. J. Immunol. 6:* 511 (1976); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Ausubel *et al.* Eds. (1989)). Likewise, the level of knowledge in the structure, characteristics, and selection of motifs relevant to signal transduction cascades is well developed and well known in the field of signal transduction research (*see, e.g.* Kemp *et al., Trends in Biochem. Sci. 15:* 342-46 (1990); Kemp *et al., Methods in Enzymology 200:* 62-81 (1991); Songyang *et al., Mol. Cell Biol. 16:* 6486-493 (1996); al-Obeidi *et al., Biopolymers 47:* 197-223 (1998); *see also* L. Cantley, overview in Cell Signaling Technology, Inc. 2000-2001 Catalogue at p. 198 -- each of these exemplary references contains many examples of the structures and features of typical signaling motifs). Indeed, the USPTO itself, in its Revised Interim Written Description Guidelines (*see supra.*), has recognized that antibody production is a mature and well-developed art in which the level of skill and predictability is high. A skilled artisan would thus readily recognize that Applicants were in possession of the presently claimed subject matter. *See* MPEP §2163(3)[a] and (3)[a](ii), MPEP 2163.02, and cases cited above.

Accordingly, Applicants have met the written description requirements of 35 U.S.C. §112, and the present rejections should be withdrawn.

§112, 2ND PARAGRAPH REJECTIONS

The previous Examiner has rejected claims 27-33 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The previous Examiner asserts that (a) claim 27 is indefinite because it is unclear if the phrase "cell signaling proteins within a genome" is intended to have the same meaning as "cell signaling proteins from genes within a genome," and (b) in claims 27, 28, and 32 the phrase "peptides or proteins with said genome" is not clear because a genome comprises of nucleic acid and not peptides. Applicants disagree, and submit that the previous Examiner has failed to construe the language of the claims from the view of those of ordinary skill in the art of antibody production, to whom they are readily clear and definite.

The rejection of claim 27 is now moot, since Applicants have voluntarily cancelled that

claim to focus on the subject matter of genus claim 28.

Definiteness of claim language must be analyzed, *not in a vacuum*, but in light of: (a) the context of the entire specification, (b) the teachings of the prior art, and (c) the claim interpretation that would be given by one ordinary skill in the relevant art. *See* MPEP §2173.02. The central inquiry is whether one of ordinary skill in the art can interpret the metes and bounds of the claims and understand what is claimed. *See Id., citing Morton Int'l. v. Cardinal Chem. Co.* (Fed. Cir 1993); *see also Amgen v. Chugai Pharmaceutical* (Fed. Cir. 1991). In determining whether the language of a claim would be clear to one of skill in the art, an examiner should *not* focus on whether more suitable language or modes of expression are available. *See* MPEP §2173.02. The language selected by the applicant need only define the subject matter with a *reasonable degree* of particularity. An examiner should not reject claims or insist on their own preferences if the language selected by the Applicant reasonably apprises the skilled artisan of what is claimed. *See* MPEP §2173.02.

Here, the language selected by Applicants to define the claimed subject matter reasonably apprises those of ordinary skill in the art of antibody production of what is claimed, hence the claims are definite. Applicants have chosen to use the claim phrase "a plurality of peptides or proteins within a genome" to indicate a feature of the claimed class of antibody, namely, the ability to bind multiple peptides or proteins expressed from the genome of a given organism. The skilled artisan is well aware that the term "genome" means all the genetic material of a particular organism. *See, e.g.* The Life Sciences Dictionary (http://biotech.icmb.utexas.edu). It is basic scientific knowledge – and well known to those of skill in the art of making and using antibodies against proteins – that genes encode proteins, and that the latter are expressed from the former. *See, e.g.* MOLECULAR BIOLOGY OF THE CELL, 2nd Ed., Chapter 5 ("Basic Genetic Mechamisms"), Garland Pub. (1989). Accordingly, the skilled artisan readily understands that the phrase "peptides or proteins within a genome" means peptides or proteins expressed from the genes of a given organism. Applicants need not explicitly say what is common knowledge in the field. Accordingly, since those of ordinary skill in the art can readily understand the metes and bounds of the claims and what subject matter is claimed, the claims are definite. The indefiniteness rejections are therefore improper, and Applicants respectfully request that the rejection of claims 28-33 be withdrawn.

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§102 REJECTIONS

(I). The previous Examiner has rejected claims 27-33 under 35 U.S.C. §102(e) as allegedly being anticipated by Tani *et al.* (U.S. Patent No. 6,001,580 issued December 14, 1999) (hereinafter the " '580 patent"). Micelli *et al.* (*J. Immun. Method. 167:* 279-287 (1994) (hereinafter "Micelli") is further cited as allegedly teaching the "generally motif-specific, context-independent nature of antibody-antigen binding." The Examiner asserts that the anti-ERK1 and ERK2 site-specific antibodies disclosed in the '580 patent are both motif-specific and context-independent, and therefore the presently claimed class of antibodies is not novel. Applicants disagree, and submit that the previous Examiner has not properly construed the claimed subject matter based on the teachings of the specification (as understood by those of skill in the art), thereby improperly concluding that the cited patent discloses all elements of the claimed subject matter.

It is well established that for a cited reference to anticipate a claimed invention it must teach *each and every element* of the claimed subject matter; the so-called "all elements" rule. *See* MPEP §706.02; MPEP §2131, *citing Verdegaal Bros. v. Union Oil of Cal.* (Fed. Cir. 1987). The first step, in determining whether a prior art reference discloses each and every element, is to properly construe the claimed subject matter. *See Helifix Ltd. V. Blok-Lok* (Fed. Cir. 2000). Proper construction of the claim requires that an Examiner closely review the entire specification to determine how an Applicant has defined and used the terms of claimed subject matter, with further consideration of what interpretation those of skill in the art would give the claim terms in view of the disclosure. *See* MPEP §2111, *citing In Re Cortright* (Fed. Cir. 1999); *see also, e.g. Pitney Bowes v. Hewlett-Packard* (Fed. Cir. 1999). It is, therefore, improper for an examiner to supplant the meaning of a term provided by an applicant and understood by skilled artisans with the examiner's own interpretations, or to read limitations or interpretations of external references into a claim.[1]

Here, the previous Examiner, in asserting that the '580 patent anticipates the presently claimed invention, has failed to first properly construe the terms of the claims in view of

[1] As the previous Examiner has improperly done by ignoring the term meanings and usage provided by Applicants' entire specification (and understood by those of skill in the art of signaling research and antibody production), and instead improperly relying on meanings crafted from the limited and off-point disclosures of Micelli and the '580 patent.

Applicants' disclosure, or with regard to their meaning to those of skill in the art. As noted above, the presently claimed invention, in its broadest sense (*see* claim 28), is a genus of antibodies having the following defining features: their binding affinity is "motif-specific" but also "context-independent," they bind either a "kinase consensus substrate motif" or a "protein-protein binding motif," the bound motif comprises "at least one phosphorylated amino acid," and they bind (*i.e.* recognize) a "plurality of peptides or proteins within a genome that contain [the] motif."

As discussed at length in the Background section of the specification, Applicants' invention solves the limitations of prior attempts to produce broadly reactive yet modification-specific antibodies desirable for research of signal transduction cascades. Prior to the present invention, individual antibodies capable of specifically binding a desired signal transduction motif, such as a phosphorylated kinase consensus substrate motif, in many different proteins expressed in an organism that contain the recurring motif simply have not been available. Applicants have now provided both a novel class of motif-specific and context-independent antibodies, and a highly reproducible method for producing them.

A careful and thorough review of Applicants *entire* specification readily indicates that what Applicants mean by "motifs" are short, modifiable (*e.g.* phosphorylatable) amino acid motifs that are conserved among multiple different proteins in signal transduction cascades (*see, e.g.*, p. 7, lines 1-24). Motifs within the scope of the present invention include single modified amino acids, such as acetylated lysine, or short motifs comprising multiple invariant (or fixed) amino acids including at least one modified amino acid, such as kinase consensus substrate motifs (*see, e.g.* p. 8, lines 5-14), which are frequently, but not always, degenerate (*i.e.* contain variable amino acid positions within the conserved motif). Such short recurring motifs are distinct from the longer, non-recurring, typically unique modified *epitopes* bound by traditional *site-specific* antibodies (*see, e.g.*, Czernik *et al.*, cited in Background section). Site-specific antibodies are typically raised against peptide epitopes of 12 or more amino acids (*see Id.*). Such epitopes, because they are significantly longer than recurring signal transduction motifs, are usually unique to a particular protein (and its close homologues, if any) and are not found in multiple different proteins within a genome. Further, although such epitopes may be modified, they do not serve as recurring consensus sites for signaling enzymes, such as kinases, nor as

recurring protein-protein binding motifs. Thus, site-specific antibodies (if they are in fact specific) normally only bind to the single target protein and epitope for which they are designed to bind; they are not capable of, nor useful for, binding multiple different proteins having a common signal transduction motif. In this respect – and in contrast to the antibodies of the present invention -- they are not "context-independent" because, in fact, their binding to the target protein is target- (and therefore, context–) *dependent*. In contrast, motif-specific, context-independent antibodies, as defined and described throughout the specification by Applicants, are designed to, and are capable of, specifically binding a recurring motif conserved among multiple different proteins, despite the differing protein contexts in which the small motif is presented to the antibody. Site-specific antibodies do not share this feature or function.

Those of ordinary skill in the art of signal transduction research and the production and use of antibodies readily appreciate the differences between what a "motif" and an "epitope" (or "site") are. Signal transduction "motifs," such as kinase consensus substrate motifs, have been well described and reviewed. *See, e.g.* Kemp *et al.*, (1990); Kemp *et al.*, (1991); Songyang *et al* (1996); al-Obeidi *et al.*, (1998); and L. Cantley, *supra.* (each of these exemplary references contains many examples of the structures and features of typical signaling motifs). Similarly, those of skill in this art readily understand what a "site-specific" antibody is, and how the epitopes bound by such antibodies differ from motifs. *See, e.g.* Czernik (1991) and Czernik (1995),; ANTIBODIES: A LABORATORY MANUAL; CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (1989), *supra.* Accordingly, the skilled artisan, having thoroughly read Applicants' specification, readily understands the features and characteristics of the class of "motif-specific, context-independent" antibodies encompassed by the present claims, and how this claimed class of antibodies differs from prior art site- or epitope-specific antibodies. The claimed subject matter and entire specification supporting it concerns not site- or epitope-specific antibodies, but rather a distinct and novel class of motif-specific, context-independent antibodies that bind short, modified, recurring signal tranduction motifs found in multiple different proteins within a genome.[2]

[2] The previous Examiner cites Micelli as allegedly teaching the "generally motif-specific, context-independent nature of antigen-antibody binding." The Examiner misreads and generalizes the limited teachings of Micelli (which teaches no such thing) while disregarding Applicants' own disclosure with respect to the "motif-specific" and "context-independent" characteristics of the antibodies of the invention. Micelli discloses nothing more than a

Turning to the cited '580 patent, entitled "Method for Assaying ERK2 MAP Kinase," the reference merely discloses the production of a traditional site-specific anti-peptide antibody that binds the kinase ERK1, and its homologue ERK2, only when phosphorylated at a particular epitope. This antibody was generated by standard anti-peptide antibody methods (described in Czernik *et al, see supra.*), and is another example of the kind of limited prior art antibodies discussed and distinguished by Applicants in the Background section of the present application. Specifically, the '580 patent discloses an anti-peptide antibody produced against a 12 amino acid long synthetic phospho-peptide, His-Thr-Gly-Phe-Leu-Thr*-Glu-Tyr*-Val-Ala-Thr-Arg (*=phosphorylated residue), which corresponds to a unique epitope present in ERK1 kinase (at residues 197-208; see Fig. 6) and its homologue ERK2 kinase (at residues 180-191; see Fig. 11). This epitope was specifically chosen because it was known to be identical in both homologues of ERK kinase. *See* column 10, lines 50-65; see also Example 6, column 24.

This ERK phospho-epitope is *not* a motif within the meaning and scope of the present claims. There is nothing in the '580 patent that indicates this epitope is conserved among any other proteins than the homologues, ERK1 and ERK2, which are essentially the same protein. Indeed, the '580 patent discloses that these two MAP kinase species are highly homologous (84.7%), and have never been shown to be different in either function or activity. *See* column 1, lines 26-34. Indeed, the 13 amino acids following this epitope are *identical* in homologues

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characterization of the binding preference of a single anti-peptide FLAG monoclonal antibody (M2) using random peptide libraries as substrates. This characterization showed that the FLAG antibody, which was raised against a 13-amino acid peptide (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys-Gly-Pro-Lys-Lys-Gly), is in fact not specific for this entire sequence, but instead preferably binds various peptides that maintain the Tyr-Lys-Xaa-Xaa-Asp sequence (called a "putative core motif") present in the immunizing peptide. Micelli in no way discloses that the observed binding preference of this single monoclonal antibody are in any way indicative or representative of general antibody-antigen binding characteristics, much less of any other antibody in particular. Indeed, the assertion made by the Examiner is contradicted by the established recognition in the art (*see* references discussed and cited in the Background section of the present specification) that typical anti-peptide (or site-specific) antibodies are in fact context-*dependent* since they only bind the target epitope and protein against which they are produced (an example is the ERK1/2 site-specific antibody disclosed in the cited '580 patent).

Furthermore, the M2 antibody disclosed in Micelli does not bind a "motif" within the scope and meaning of the present invention and claims; there is no indication that the "putative core motif" preferred by the M2 antibody is relevant to signal transduction nor conserved among signaling proteins. Unlike the antibodies of the present invention, the antibody disclosed in Micelli is not truly "specific" for the sequence against which it was raised, since the antibody in fact binds other peptides *not* having that sequence. (See Figure 1). The preferred core motif described in Micelli (see p. 282, second column) does not contain any phosphorylated amino acids, nor is it a kinase consensus substrate motif nor a protein-protein binding motif, nor a single modified amino acid. Micelli, therefore, in no way anticipates the presently claimed subject matter nor supports the proposition asserted by the previous Examiner.

ERK1 and ERK2 (compare residues 209-221 in Fig. 6 to residues 192-204 in Fig. 11), while 11 of the 13 amino acids preceding this epitope are *identical* in these homologues (compare residues 184-196 in Fig. 6 to residues 167-179 in Fig. 11). Accordingly, the antibody disclosed in the '580 patent is not context-independent, as the ERK1 and ERK2 context surrounding the bound epitope is, in fact, essentially identical. Lastly, there is nothing in the '580 patent to indicate that the disclosed antibody is capable of binding to a plurality of different proteins or peptides within a genome that contain a motif. Rather, the '580 patent merely discloses a site-specific antibody that binds an epitope that is conserved between two highly homologous variants of the same protein. Accordingly, the cited disclosure fails to disclose an antibody meeting each and every limitation of the claimed subject matter, and the present rejections should be withdrawn.

Moreover, claim 28 (and claims dependent thereon) further requires that the antibody bind a kinase consensus substrate motif or a protein-protein binding motif. The antibody disclosed by the cited '580 patent is neither. Rather, the '580 patent merely states that the epitope against which the antibody was raised is present in both homologues, ERK1 and ERK2, and must be phosphorylated at two residues in order to active this protein (itself a kinase). *See* column 1, lines 26-34 and 54-59. The '580 patent does not disclose an antibody specific for a kinase consensus substrate motif (*i.e.* a short motif common to multiple different proteins that is a consensus site for enzymatic modification by a particular kinase) nor a protein-protein binding site. Accordingly, the cited '580 patent further fails to disclose an antibody meeting each and every limitation of the claimed subject matter, and the present rejections should be withdrawn.[3]

Lastly, in order for a prior art reference to anticipate a claimed invention, it must describe and enable the claimed invention in sufficient detail to have placed it in the possession of a person of ordinary skill in the relevant art. *See, e.g., Helifix Ltd. v. Blok-Lock* (Fed. Cir. 2000);

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[3] The previous Examiner hypothesizes, without providing any evidence or factual support, that the antibodies of the cited '580 patent are "presumed to be structurally and functionally indistinguishable from those encompassed by the presently claimed antibodies" (*see* Feb. 25th Office Action at p. 7, third paragraph). Such unsupported postulation is not only impermissible, but is contradicted by the evidence of record. As discussed at length, a thorough reading of Applicants' disclosure and the cited '580 patent readily reveals the many distinctions between the antibodies disclosed in both. The ERK monoclonal antibody disclosed in the '580 patent is neither "motif-specific" nor "context-independent" within the meaning and scope of the present claims. Rather, it is simply another example of prior art phospho-epitope-specific antibodies that are distinct from the novel class of antibodies presently claimed, and not useful for the same purposes for which the claimed antibodies are useful.

Motorola Inc. v. Interdigitial Technology Corp. (Fed. Cir. 1997). The disclosure of the cited '580 patent fails to satisfy this requirement. The presently claimed subject matter, in its broadest sense, is a novel class of antibodies that are both motif-specific, and context-independent; they are designed to be, and are capable of, binding multiple different proteins within a genome that contain a common, short, modified motif relevant to signal transduction. The production of these novel antibodies was only made possible by Applicants' invention of a new method for creating these antibodies using degenerate peptide libraries as immunogens. The rationale for this method and its practice are described in great detail in the specification. *See, e.g.* p. 12, line 21 to p. 19, line 20, generally. Production of a motif-specific antibody by this method ensures the context-independence of the resulting antibody, and its ability to bind many different proteins containing the target motif. *See, e.g.* p. 24, lines 16-26; p. 13, lines 4-10.

The '580 patent, in contrast, not only fails to disclose the existence of a motif-specific, context-independent antibody as presently claimed, but provides absolutely no teaching of how to produce or use antibodies of the present invention. Rather, the '580 patent merely discloses a traditionally produced site-specific anti-peptide antibody that binds a unique phosphorylated epitope present in both homologues of ERK kinase. The '580 patent does not describe nor enable Applicants' claimed invention in sufficient detail to place those of skill in the art (of signal transduction research and antibody production) in possession of it. Accordingly, the subject matter of pending claims 28-33 and 39 is novel over the cited reference, and the rejections should be withdrawn.

(II). The previous Examiner has also rejected claims 27-33 under 35 U.S.C. §§102(a) and (e) as allegedly being anticipated by Strulovici (U.S. Patent No. 5,759,787, issued June 2, 1998) (hereinafter the " '787 patent"). The Examiner asserts that the '787 patent discloses (i) a monoclonal antibody, YC10, that binds a phosphorylated motif that is a consensus motif for PKA kinase, and (ii) antibodies that bind phosphorylated epitopes on mitotic proteins and/or single phosphoresidues, which antibodies allegedly anticipate the presently claimed subject matter. Applicants disagree, and submit – as set forth in detail above – that the previous Examiner has misconstrued the meaning and scope of the present claims, and mis-read the

teachings of the cited reference.[4] The antibodies disclosed in the '787 do not, in fact, meet each and every element of the present claims.

The '787 patent, entitled "Kinase Assay," discloses nothing more than methods for detecting the activity of kinases upon peptide substrates in an immobilized assay. Among the Examples provided in the '787 patent is the use of the commercially available anti-GFAP (glial fibrillary acidic protein) antibody, YC10, to detect phosphorylation of a substrate peptide (RRRVTSAARRS, peptide #2) by PKC or PKA kinase; the substrate peptide corresponds to the GFAP epitope (residues 7-12 of GFAP) that is phosphorylated *in vivo* by these kinases. (*See* YC10 Antibody Product Data Sheet (Cat. No. NBA-115), Stressgen Bioreagents, www.stressgen.com). This antibody, a typical site-specific antibody that binds only GFAP when phosphorylated at serine 7, was raised against the following 11 residue peptide: R-R-R-V-T-phosphoSer-A-A-R-R-phosphoSer (*See id.*). GFAP is an intermediate-filament, or structural protein, that is a marker of astrocyte cell maturation. (*See id.*)

The YC10 antibody used in the '787 patent is not a "motif-specific" antibody within the meaning and scope of the present claims. Rather, it is a typical site-specific antibody that only binds to a specific phosphorylation site in GFAP, the protein for which it is intended to be specific (test peptide #2 employed in the '787 patent is identical to the phosphorylation site in GFAP (residues 3-13) (*see* YC10 Product Data sheet, *supra.*, and '787 patent column 6, line 8). There is no teaching in the '787 patent that the sequence bound by the YC10 antibody is a signal transduction motif conserved among different signaling proteins. Indeed, GFAP is a structural protein. The sequence bound by YC10 contains a phosphoserine residue, but the '787 patent does not disclosure that it is a "kinase consensus substrate motif or protein-protein binding motif" within the scope of the present claims. Rather, the '787 patent merely states that the GFAP site for which the YC10 antibody is specific is phosphorylatable by PKA or PKC, not that this site is in any way a recurring or consensus site. There is no disclosure in the '787 patent (nor in the YC10 product data sheet) indicating that this antibody is capable of binding any other protein, much less a plurality of proteins or peptides within a genome, as required by the present

[4] The previous Examiner has again relied on Micelli as teaching that all antibody-antigen binding is "motif-specific" and "context-independent" within the meaning of the present specification and claims. The Examiner's interpretation of Micelli is incorrect, and his reliance on the reference is not supportable, for the reasons already set forth above (and in footnotes 2-3 above).

claims. Thus, YC10 is not a "context-independent" antibody within the meaning and scope of the present claims. The site-specific YC10 antibody employed in the cited '787 patent does not meet all the limitations of the present claims, and therefore does not anticipate the claimed subject matter.

Similarly, neither the MPM-2 or 4G10 antibodies utilized in the other Examples of the '787 patent anticipate the presently claimed class of motif-specific, context-independent antibodies. The '787 patent discloses that MPM-2 is a monoclonal antibody that binds a phosphorylated epitope in mitotic proteins, but states that the exact epitope it binds is not known. *See* column 8, lines 49-53. This antibody was employed in the '787 patent to detect the phosphorylation, by CAMK II kinase, of a 39 amino acid peptide (peptide #4, see column 6, lines 13-15) that corresponds to a phosphorylation site in RIP (see column 6, line 15), itself a kinase involved in apoptosis (*see* Hsu *et al.* (1996), cited in '787 patent). The '787 patent further discloses that 4G10 is a monoclonal anti-phosphotyrosine antibody that is commercially available. *See* column 9, lines 6-7 and column 5, lines 50-51. 4G10, a well-known antibody, was produced against a phosphotyramine residue coupled to KLH (a prior art approach of limited success discussed in the Background section of Applicants' specification at p. 3, starting at line 20). This antibody was employed in the '787 patent to detect phosphorylation, by CAMK II kinase, of an 8 amino acid, biotinylated peptide (peptide #3, see column 6, lines 11-12) that corresponds to a phosphorylation site in phosphorylase kinase (*see Id.*).

Neither the MPM-2 nor the 4G10 antibodies disclosed and utilized in the '787 patent are "motif-specific" and "context-independent" antibodies within the scope and meaning of the present claims. There is no indication in the '787 patent that MPM-2 is specific for a motif conserved among multiple different signal transduction proteins, nor that this antibody is capable of binding multiple different proteins containing such a motif. Indeed, the '787 patent states that the binding specificity of this antibody is unknown. The '787 patent does not disclose that either the MPM-2 antibody or 4G10 antibody are specific for a kinase consensus substrate motif or a protein-protein binding motif. Rather, MPM-2 is disclosed as a phospho-specific antibody that binds an unspecified and unknown epitope on RIP protein, while 4G10 is disclosed as a phospho-tyrosine specific antibody. Both of these antibodies fail to meet each and every element of the present claims, and therefore do not anticipate the presently claimed subject matter.

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Finally, as previously discussed, in order for a prior art reference to anticipate a claimed invention, it must describe and enable the claimed invention in sufficient detail to have placed it in the possession of a person of ordinary skill in the relevant art. *See, e.g., Helifix, supra.*; *Motorola, supra.* The cited '787 patent not only fails to disclose the existence of a motif-specific, context-independent antibody as presently claimed, but provides absolutely no teaching of how to produce or use antibodies of the present invention. Rather, the '787 patent merely discloses a traditionally produced site-specific anti-peptide antibody (YC10) that binds a phosphorylated epitope present in a single protein, GFAP, a phospho-specific antibody (MPM-2) that binds an unspecified epitope on a single protein, RIP, and an anti-phosphotyrosine antibody (4G10) that was produced by the traditional method of coupling that residue to KLH. The '580 patent does not describe nor enable Applicants' claimed invention in sufficient detail to place those of skill in the art (of signal transduction research and antibody production) in possession of it. Accordingly, the subject matter of pending claims 28-33 and 39 is novel over the cited reference, and the rejections should be withdrawn.

Conclusion

The present claims are believed to be in condition for immediate allowance. The subject matter of the claims is patentable over the cited references, and Applicants submit that all rejections made by the previous Examiner have been overcome. Applicants respectfully request that the present claims be promptly advanced to allowance and issuance.

If there are any questions regarding these Remarks or Amendments, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,

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